Adenovirus Vaccine Restoration

Presentation to
Armed Forces Epidemiological Board

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Outline

- Program Overview
- Manufacturing
- Clinical
- Regulatory
- Quality
- Procurement
- Funding
- Near Term Plan/Events
- Program Risks

Defense Health Program Requirement

In consultation with the AFEB, ASD(HA) officially established a Defense Health Program requirement for adenovirus vaccine type 4 and type 7 to protect military recruits against adenovirus infection

Objective

Provide a safe, efficacious, FDA approved Adenovirus Vaccines (Type 4 and 7) to protect US military basic trainees from adenovirus febrile respiratory disease.

History

- 2001, contract awarded to Barr Laboratories
- 2002, technology transfer from Wyeth
- 2003, completed construction of adenovirus vaccine tablet manufacturing facility
- 2004, contract was modified to cover unanticipated redevelopment efforts and manufacturing process improvements
- 2004, Investigational New Drug (IND) application was submitted to the FDA
- Aug 04 – Jun 05, Phase 1 clinical trial was completed at Ft. Sam Houston, TX
- Aug 05, Phase 1 Clinical Study Report and Phase 3 protocol was submitted to the FDA for review
- Oct 05, FDA provided informal response to Phase 3 protocol

Development Plan-Dec 05

ID	Task Name	Start	Finish
1	**Adenovirus Vaccine, Types 4 & 7**	Mon 8/6/01	Mon 8/6/01
2	**Basic Contract**	Fri 9/21/01	Wed 11/9/05
3	**DoD Contract Award**	Fri 9/21/01	Fri 9/21/01
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5	**Wyeth Material received**	Mon 5/20/02	Mon 9/16/02
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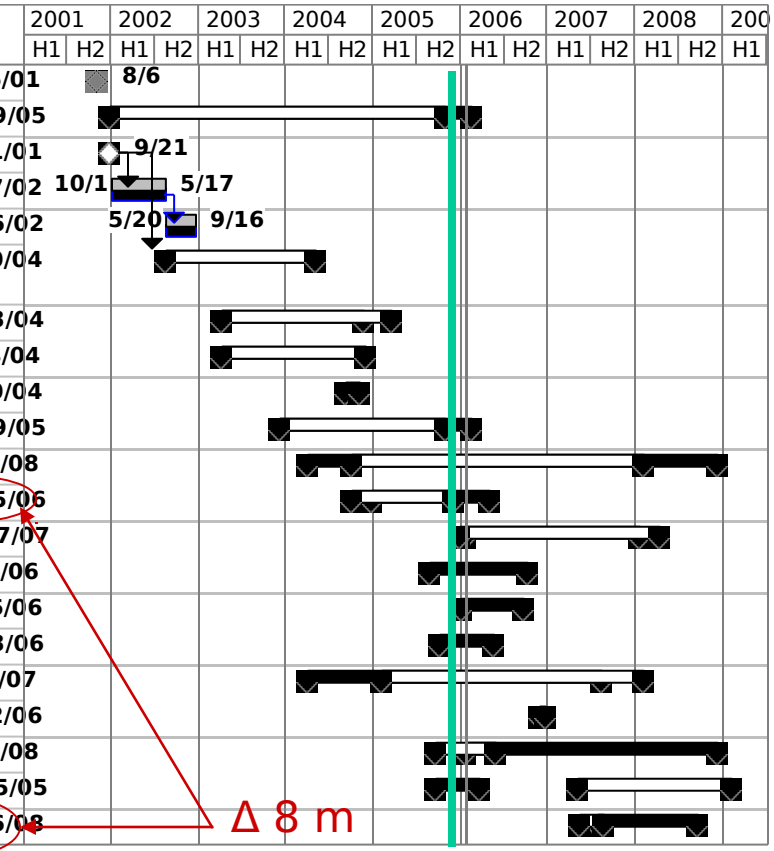
147	**VA Lyophilizer Qualification Schedule**	Tue 10/4/05	Fri 6/16/06
180	**RA activeities before next trial start**	Thu 7/7/05	Mon 2/13/06
194	**Phase II/III Clinical Trial**	Thu 1/1/04	Tue 5/8/07
257	**Write Reports**	Mon 8/28/06	Fri 9/22/06
260	**Consistency Lot Manufacturing**	Mon 10/24/05	Fri 9/5/08
288	**Quality Systems**	Thu 6/16/05	Thu 12/15/05
296	**Prepare and Submit BLA**	Mon 4/23/07	Mon 6/16/08



Vaccine Manufacturing

- Initial vaccine stability program terminated
  - Objective: Stable at 2-6° C for 2 years
  - Review found incubator had spiked above approved process temperature
  - Concurrent protocols initiated to investigate vaccine stability and formulation
  - ***Critical Path Task:*** GMP vaccine manufacturing for next clinical trial is dependent on success of stability testing
    - **Six month delay in program**

- Difficulties in scale-up production of bulk virus
  - Duramed's WI-38 Master Cell Bank depleted
  - New WI-38 Working Cell Bank (~200 vials/ 20 yrs) produced

- Lyophilizer in tablet facility has not been validated (Est. June 2006)
  - **Critical Path Task:** Demonstration of manufacturing lot consistency required prior to licensure
  - Current manufacturing plan for consistency lots is dependent validation of lyophilizer

Phase I Clinical Study

A Phase 1, Randomized, Double-Blind, Placebo Controlled Study to Evaluate The Safety And Immunogenicity Of The Live, Oral Type-4 and Type-7 Adenovirus Vaccines

Primary Objective:

1. Evaluation of the safety of type 4 and type 7 vaccines administered together.

Secondary Objectives:

1. Evaluation of the immune response (neutralizing antibody titer and seroconversion rate)

2. Characterization of the duration of virus shedding

Results:

1. Well tolerated – no safety issues

2. Seroconversion rate at Day 28
   - 72.7% (8 of 11 subjects) for ADV-4
   - 62.5% (10 of 16 subjects) for ADV-7

3. Vaccine virus found in the stool as early as Day 7, but none by Day 28

Phase 3 Clinical Study

- Propose to establish clinical efficacy of ADV 4 by case reduction and derive a protective level of antibody, then infer efficacy of ADV 7 using a similar approach using antibody correlate of protection
  - Efficacy objective: 80% effective
  - ***Scope Change:*** Change in clinical plan compared to Duramed's technical proposal

- Great Lakes NRTC and Fort Jackson were selected as primary clinical trial sites
  - Objective: Start Apr 06
  - Site visits conducted/on-going

- Start of next clinical study is dependent on:
  - Resolution of clinical trial agreement
  - Scientific and Human Safety Review Board approval of protocol (multiple IRB's)
  - Formal FDA Pre-Phase 3 meeting (Est. Jan-Feb 2006)
  - Site preparation and integration of clinical trial with the Services' training schedule

Regulatory

- Phase 1 Clinical Study Report (CSR) reviewed by FDA
  - CSR was well received, FDA teleconference on 11 AUG 05
- FDA completed protocol review and provided informal comments to draft phase 3 protocol in teleconference on 20 OCT 05
  - FDA agreed with primary and secondary endpoints for evaluation of vaccine efficacy for adenovirus type 4 and type 7
  - Clinical assays must be validated prior to start of clinical study
  - FDA suggested an increase in sample size for Phase 3 and inclusion of a nested cohort with more intense monitoring
- FDA teleconference 30 NOV 05
- Formal FDA meeting dependent on:
  - Clinical protocol
  - Additional information on product chemistry, manufacturing, and controls

Quality

- Provide quality oversight to assure vaccine manufacturing has appropriate processes and controls in place to produce safe and effective adenovirus vaccines consistently

- Assure quality systems to control the integrity of the data generated from the clinical study

Procurement

- Currently coordinating procurement and logistics plan with resource management, contracting, and logistics personnel to provide effective transition from licensure to distribution

- Vaccine cost estimate received May 2005
  - Significant increase in vaccine cost estimate from initial proposal (2001)
  - Further explanation and full cost detail was requested
  - Duramed was unwilling to provide full cost detail at this time (July, 2005)
  - Detailed vaccine cost estimate is required to establish a fair and reasonable vaccine price for procurement contract
    - The Defense Contract Audit Agency will audit Duramed Research
    - Additional negotiation is necessary to reduce life cycle cost and eliminate delay in vaccine procurement

Current Threat

Estimated adenovirus infection rates by service, 1999-2004*

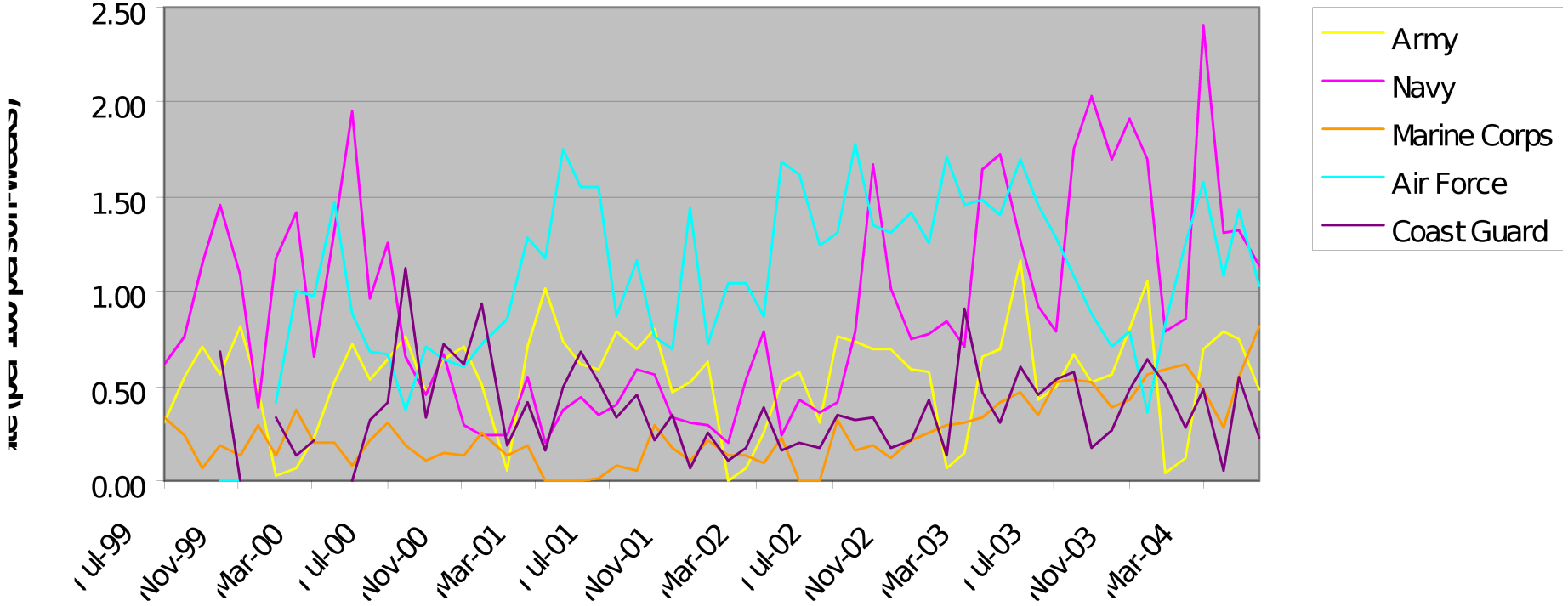


*Figure provided by CDR Russell, Naval Health Research Center

Funding

- Vaccine development effort may require additional funding
  - Cost Plus Fixed Fee contract
  - Contract scope change to support expanded Phase 3 study is anticipated

- Vaccine procurement in FY08-13 is not fully funded
  - Currently requesting full funding for FY08-13 in POM process
  - Annual cost based on ~250K doses of vaccine to vaccinate all services initial entry trainees

Moving Forward

- **Next 3 months**
  - Manufacturing
    - Additional vaccine stability testing
    - Initiate validation process for lyophilizer in tablet facility
  - Clinical:
    - Clinical Trial Agreement
    - Finalize study design
    - Initiate protocol review
    - Prepare study sites
  - Regulatory
    - Formal FDA meeting
  - Quality
    - Quality audits
  - Funding
    - Contract scope change/cost increase
    - Programming/Budgeting for procurement of vaccine

Moving Forward

- Next 3-6 months
  - Complete validation master plan and qualify manufacturing facility
  - Produce additional vaccine for demonstrating vaccine lot consistency
  - Initiate clinical protocol at approved sites

Program Risks

- Vaccine performance
- Production failures
- Further delays in CTA, protocol development, review and approval (scientific and human use)
- Regulatory (FDA) guidance
- Integration of trials with basic training schedules
- Increased cost of vaccine

Any or all of the above could impact baseline

performance, schedule, and cost

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